Lecture 15

More Carbonyl Chemistry

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March 12, 2019

Chemistry 328N

Grignard reagents react with:

formaldehyde to give primary alcohols

aldehydes to give secondary alcohols

ketones to give tertiary alcohols

esters to give tertiary alcohols

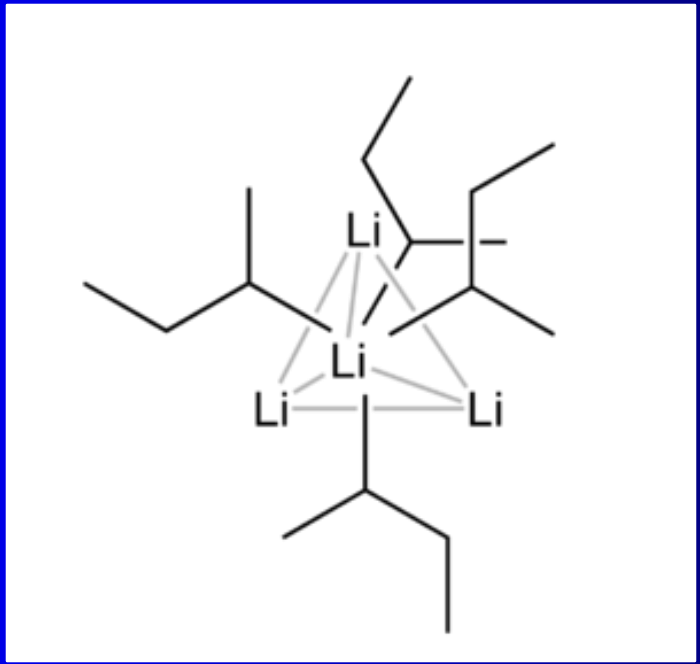
CO_2 to give acids

epoxides give primary alcohols

Organolithium Reagents

$$R\text{-}Cl + Li \xrightarrow[THF]{} RLi + LiCl$$

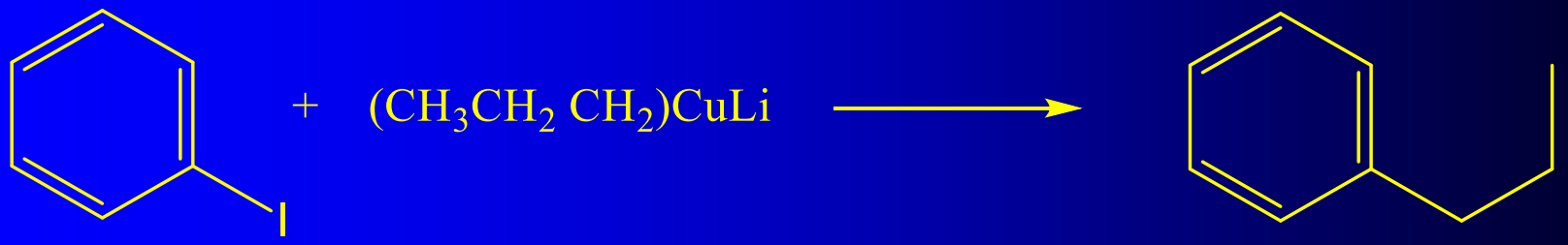
R can be alkyl aryl or alkenyl



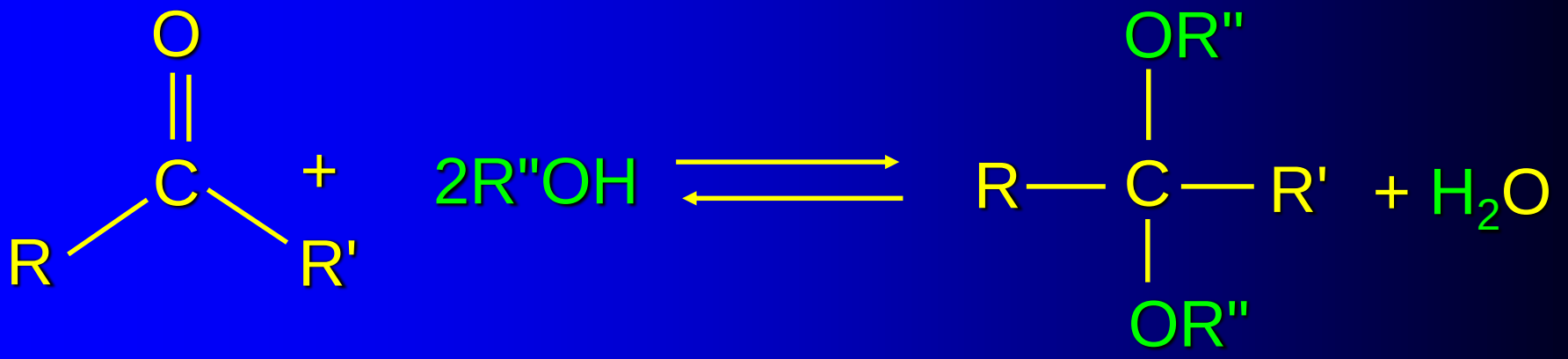
Gilman Reagents

$$2\ RLi + CuI \xrightarrow[THF]{} R_2CuLi + LiI$$

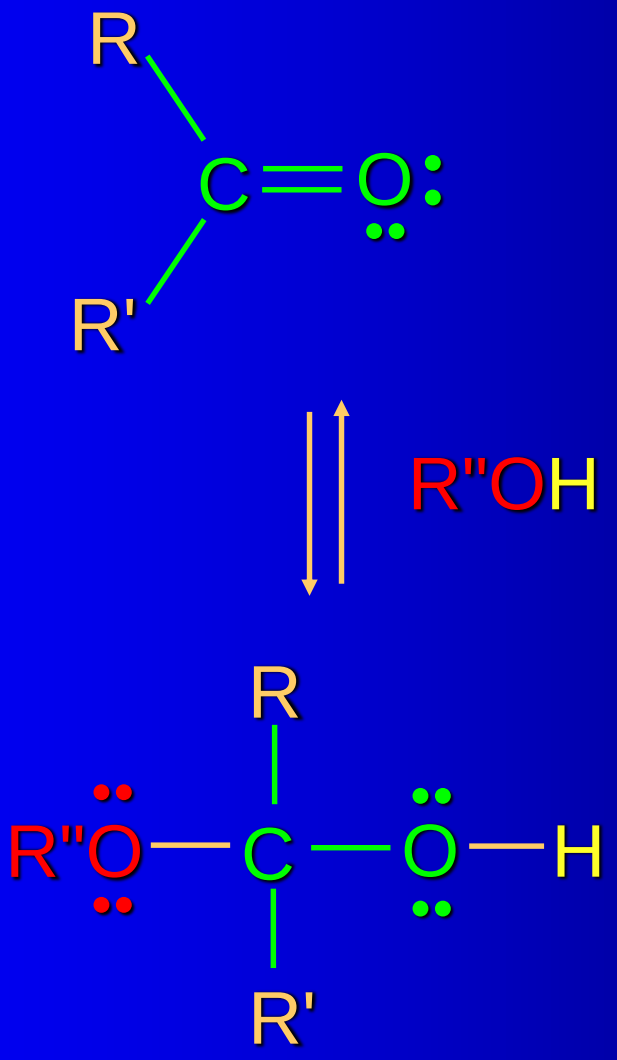
R can be alkyl aryl or alkenyl



Oxygen Nucleophiles

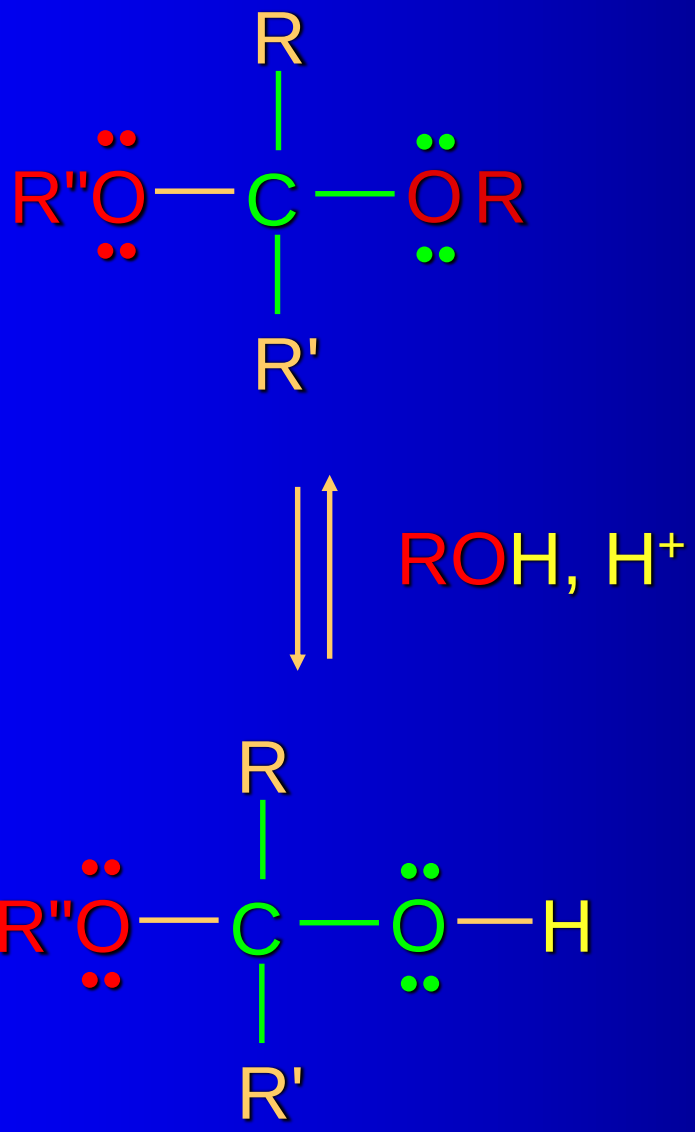


Alcohols React with Aldehydes and Ketones in two steps…first



Product is called a *hemiacetal*.

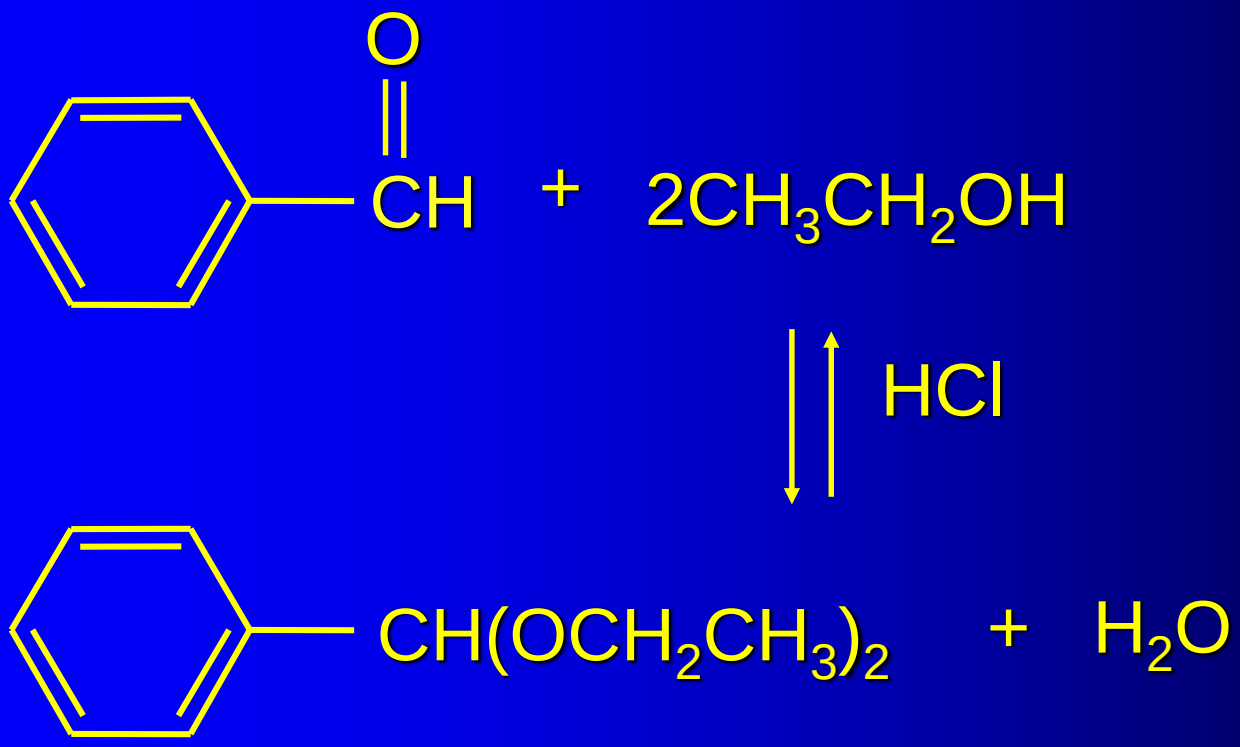
Hemiacetal reacts further in acid to yield an acetal



This product is called an *acetal*.

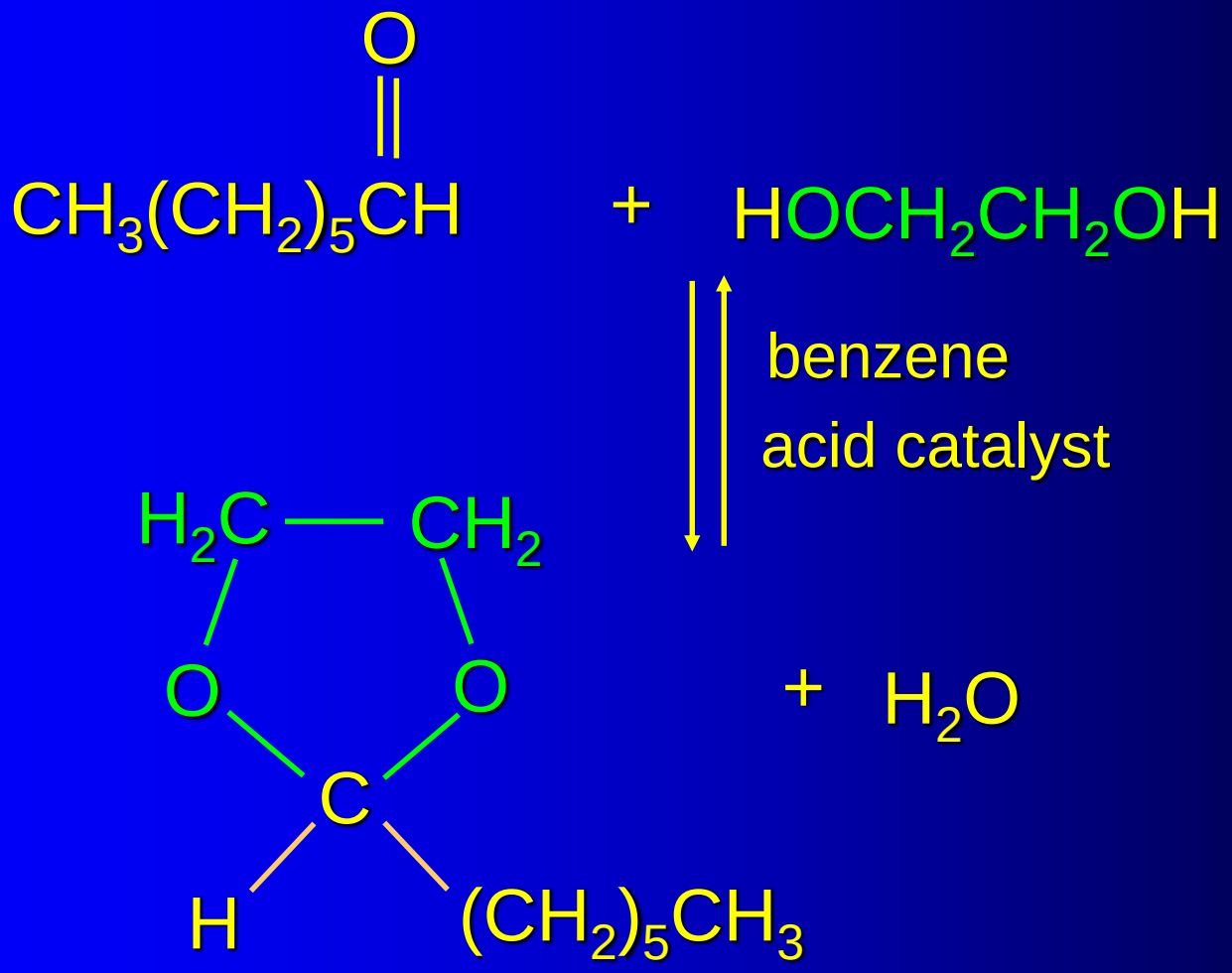
This *hemiacetal reacts further*.

Example

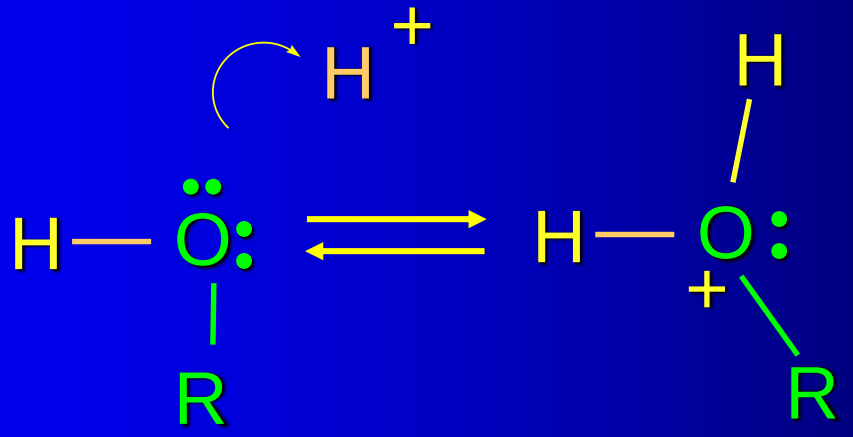


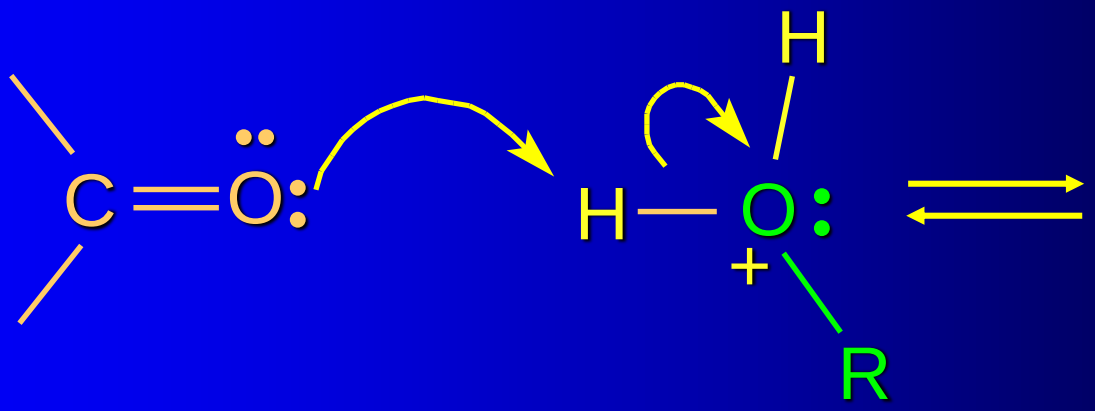
Benzaldehyde diethyl acetal

Diols Form Cyclic Acetals

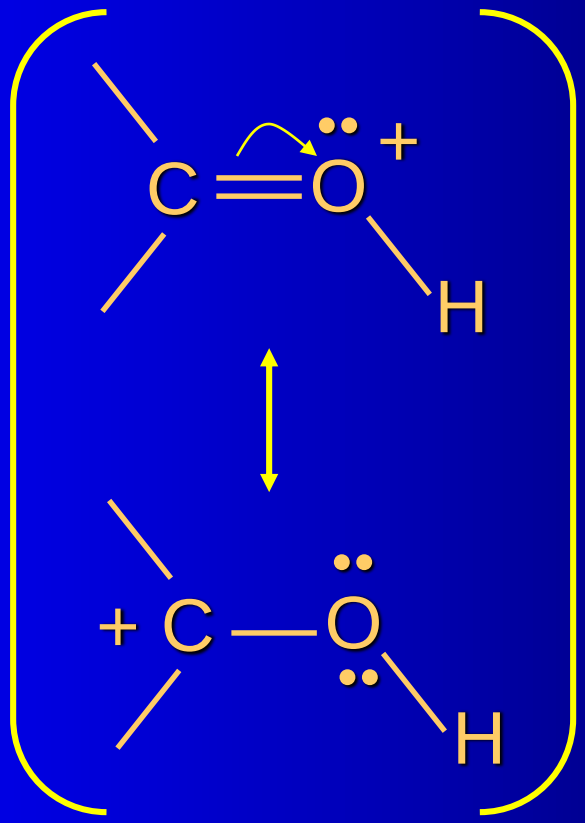


Mechanism of Acetal Formation



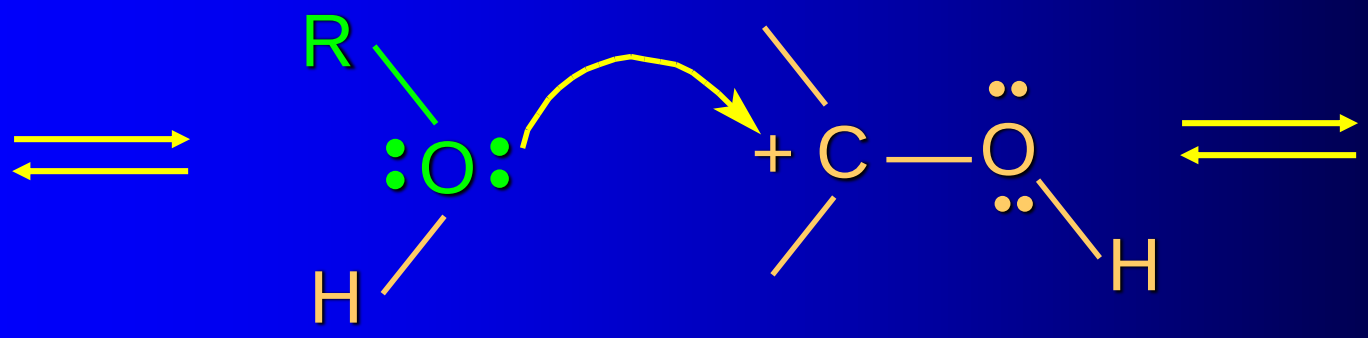


Mechanism

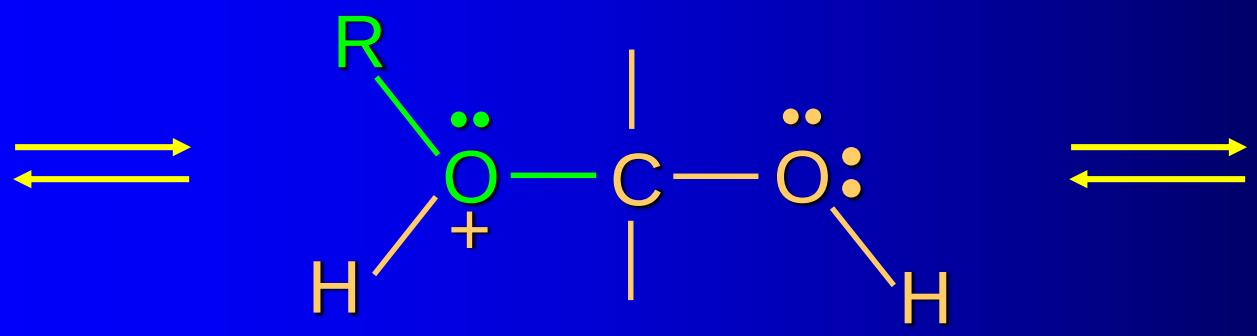


Resonance stabilized cation

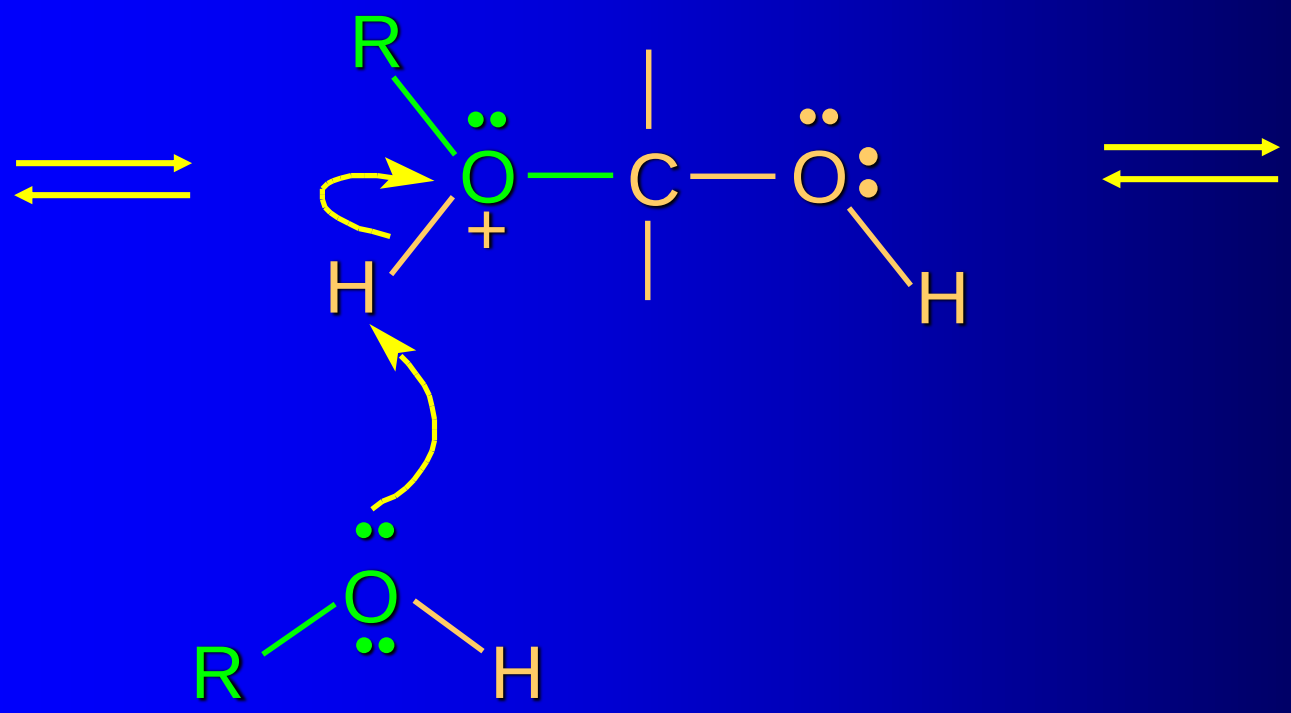
Mechanism



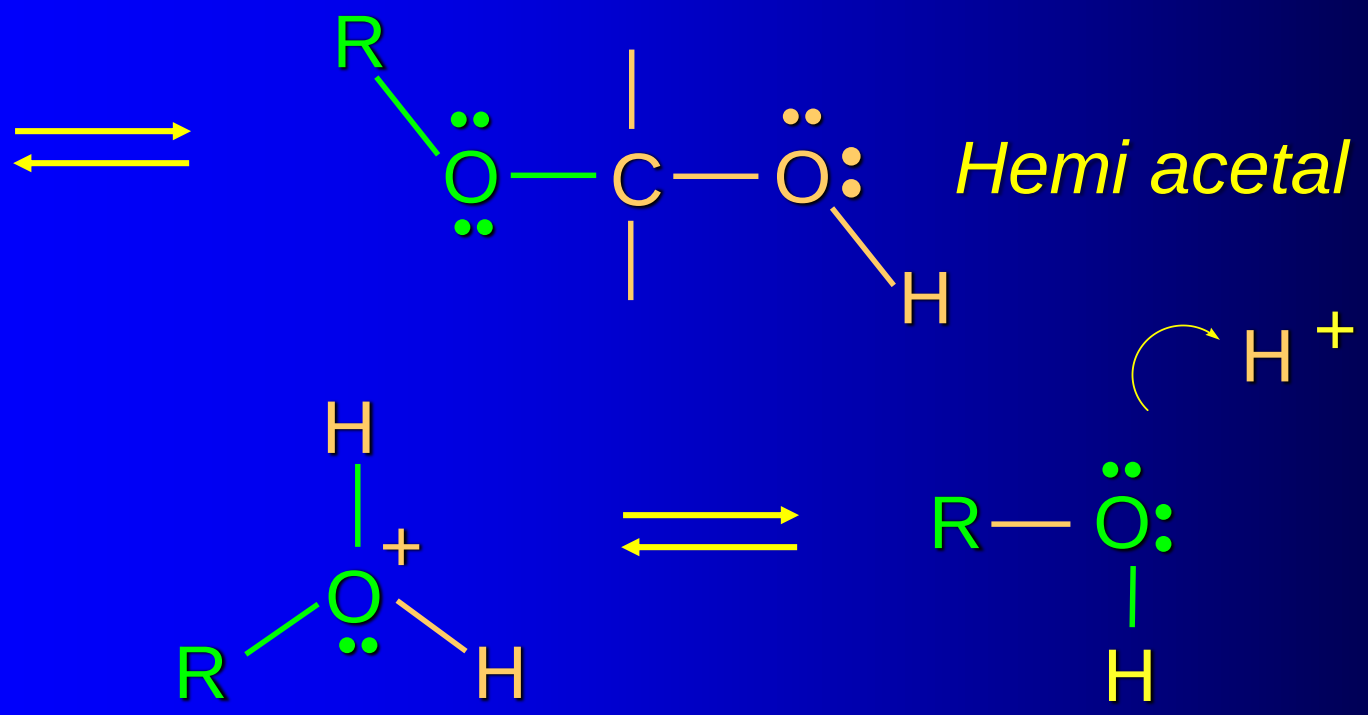
Mechanism



Mechanism



Mechanism



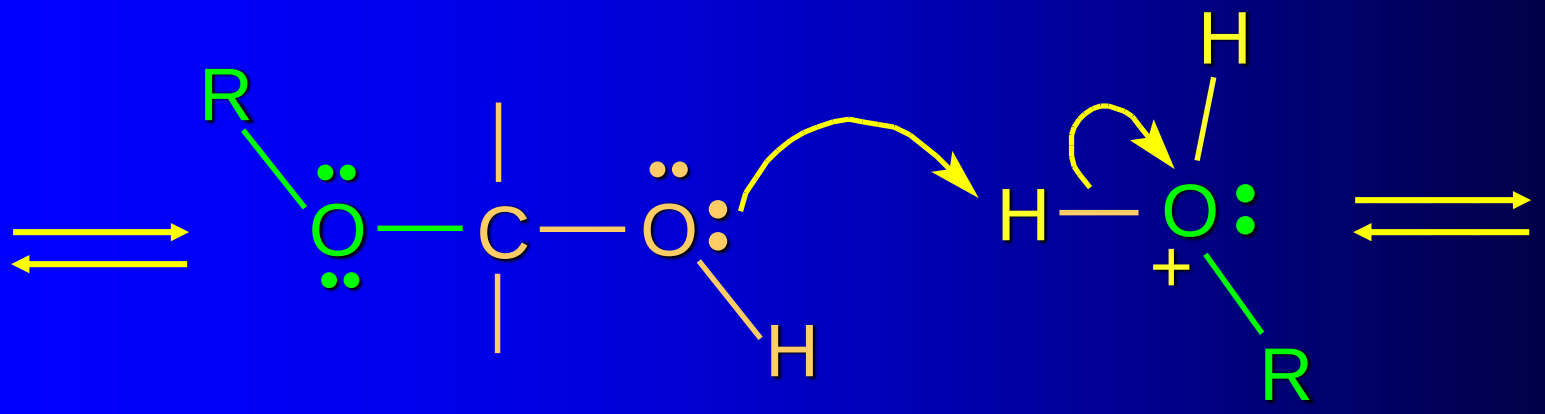
Catalyst regenerated!

Mechanism of Acetal Formation

Second stage is hemiacetal-to-acetal conversion

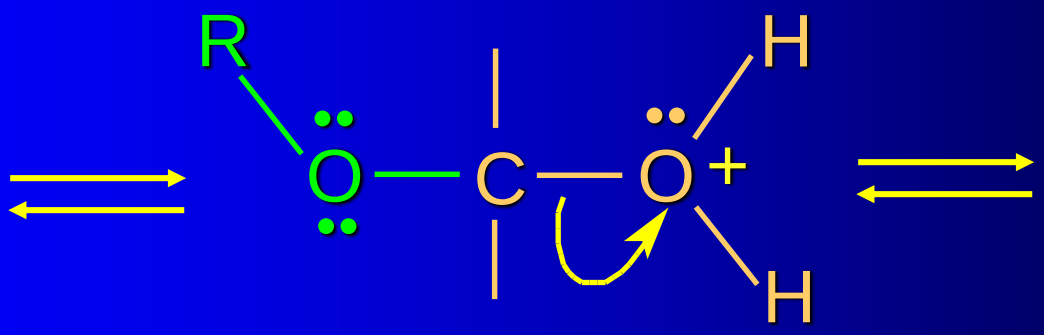
involves carbocation chemistry

Hemiacetal-to-acetal Stage

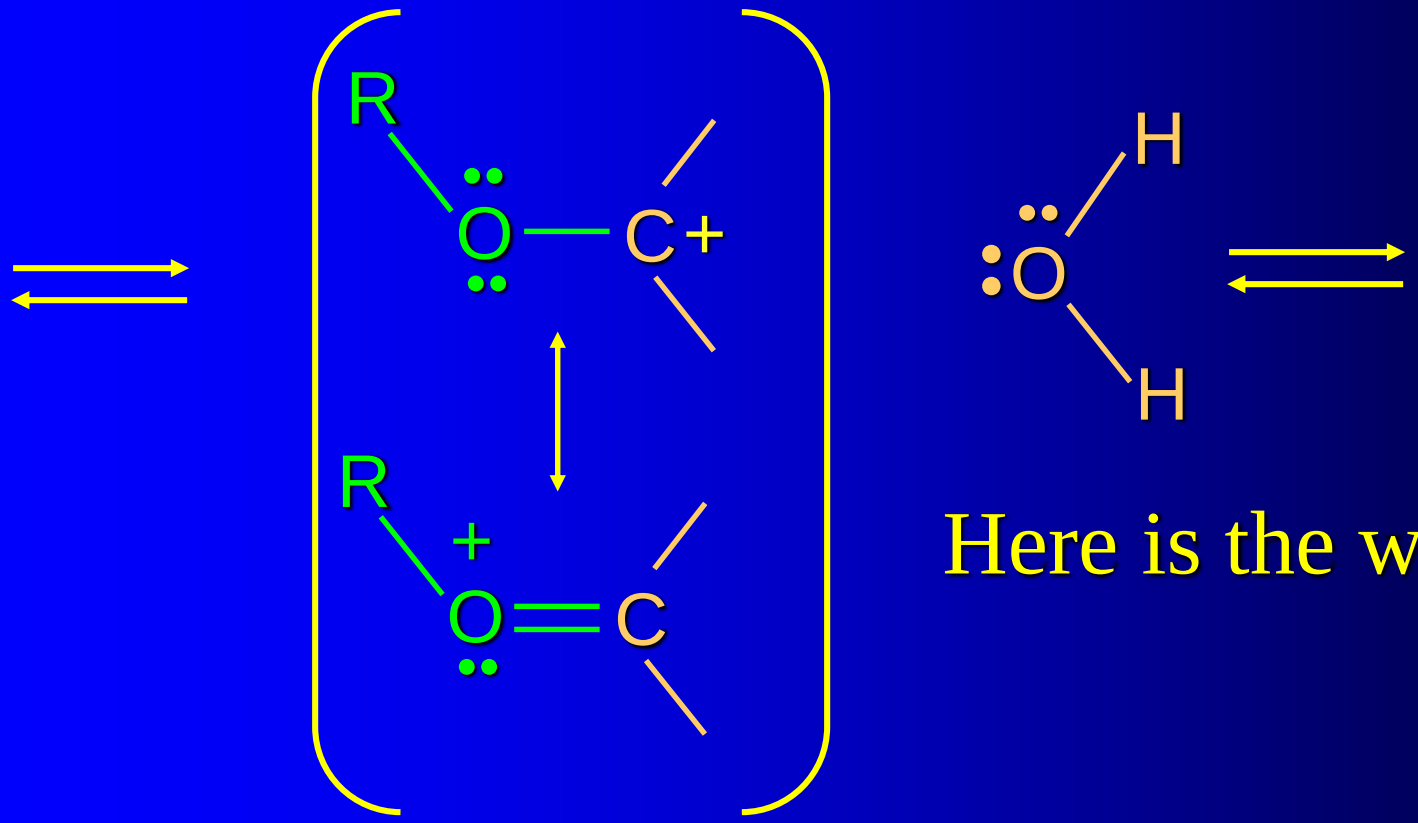


These are not separate reactions…
this is all one big equilibrium

Hemiacetal-to-acetal Stage

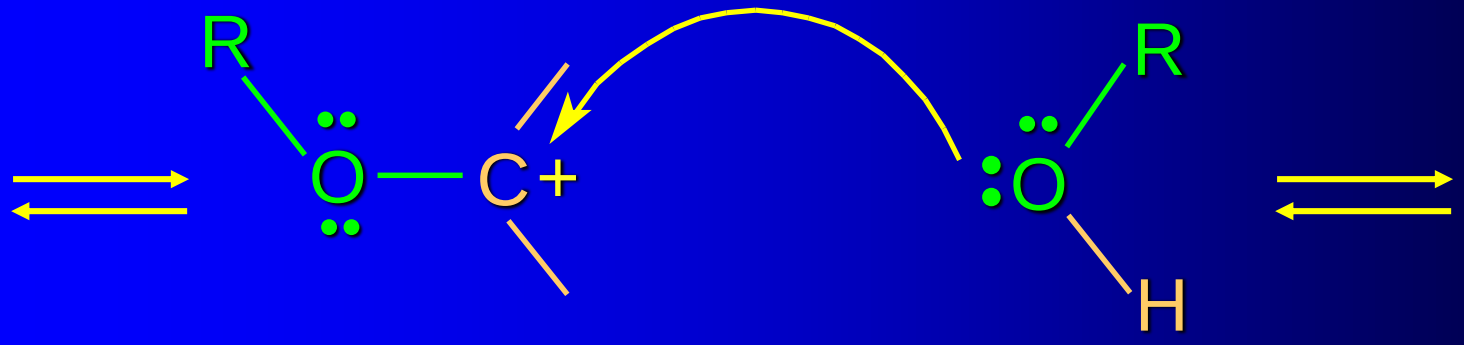


Hemiacetal-to-acetal Stage

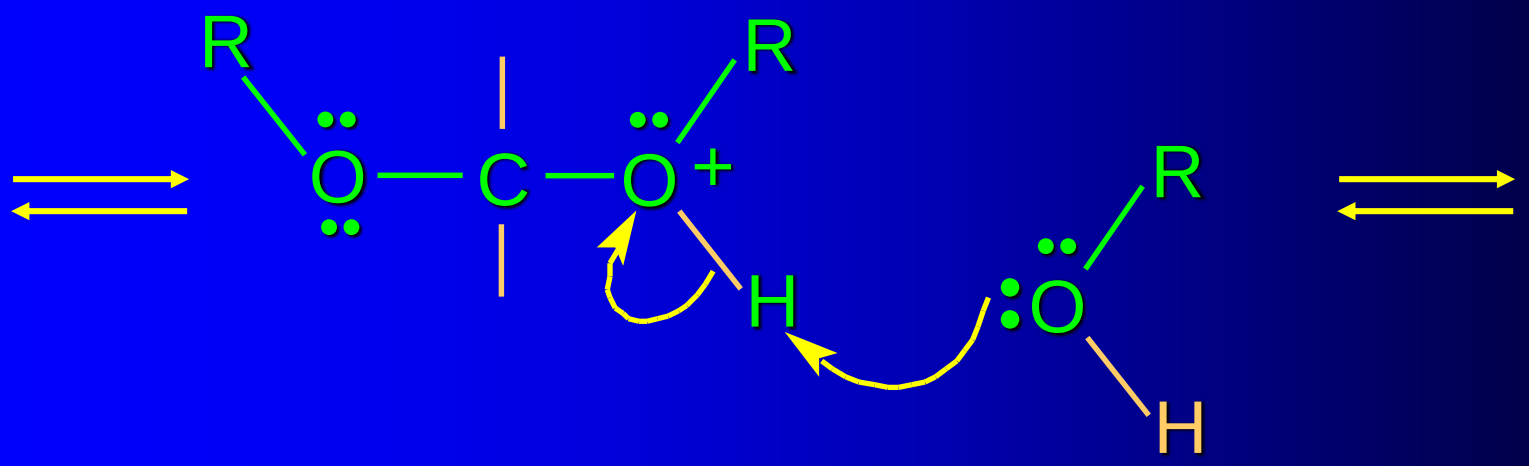


Here is the water!

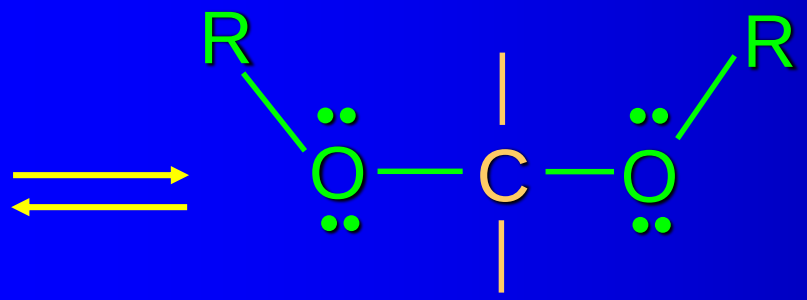
Hemiacetal-to-acetal Stage



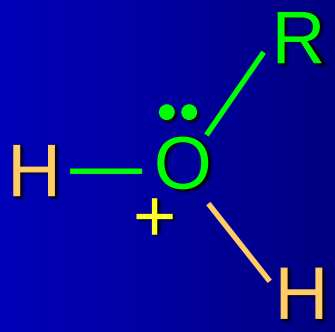
Hemiacetal-to-acetal Stage



Hemiacetal-to-acetal Stage



The acetal



Regeneration of catalyst

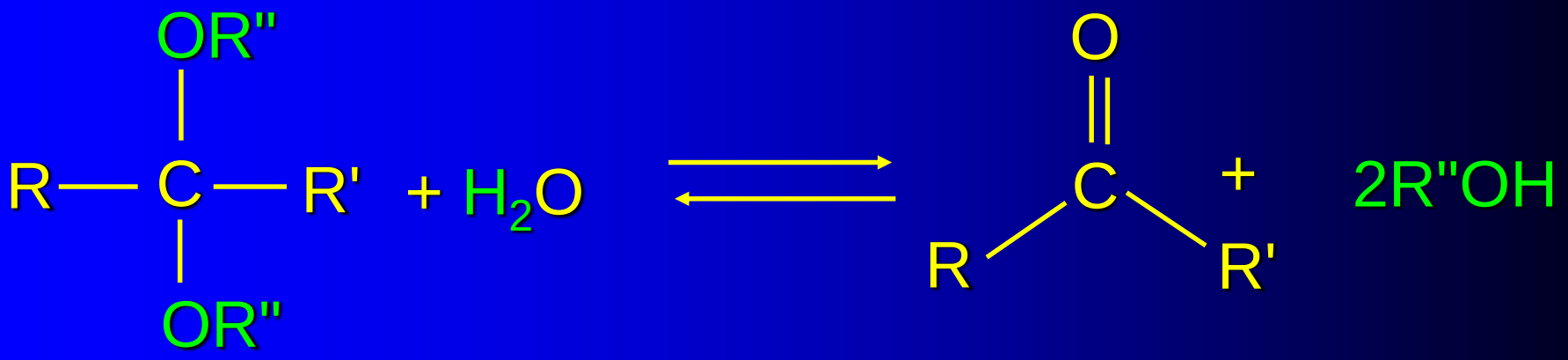
Note that EVERY step is an equilibrium

Therefore, the reaction can be pushed forward or backward by appropriate choice of conditions

The forward reaction is synthesis
The backward reaction is hydrolysis

See Page 673 - Mechanisn 16.7

Hydrolysis of Acetals

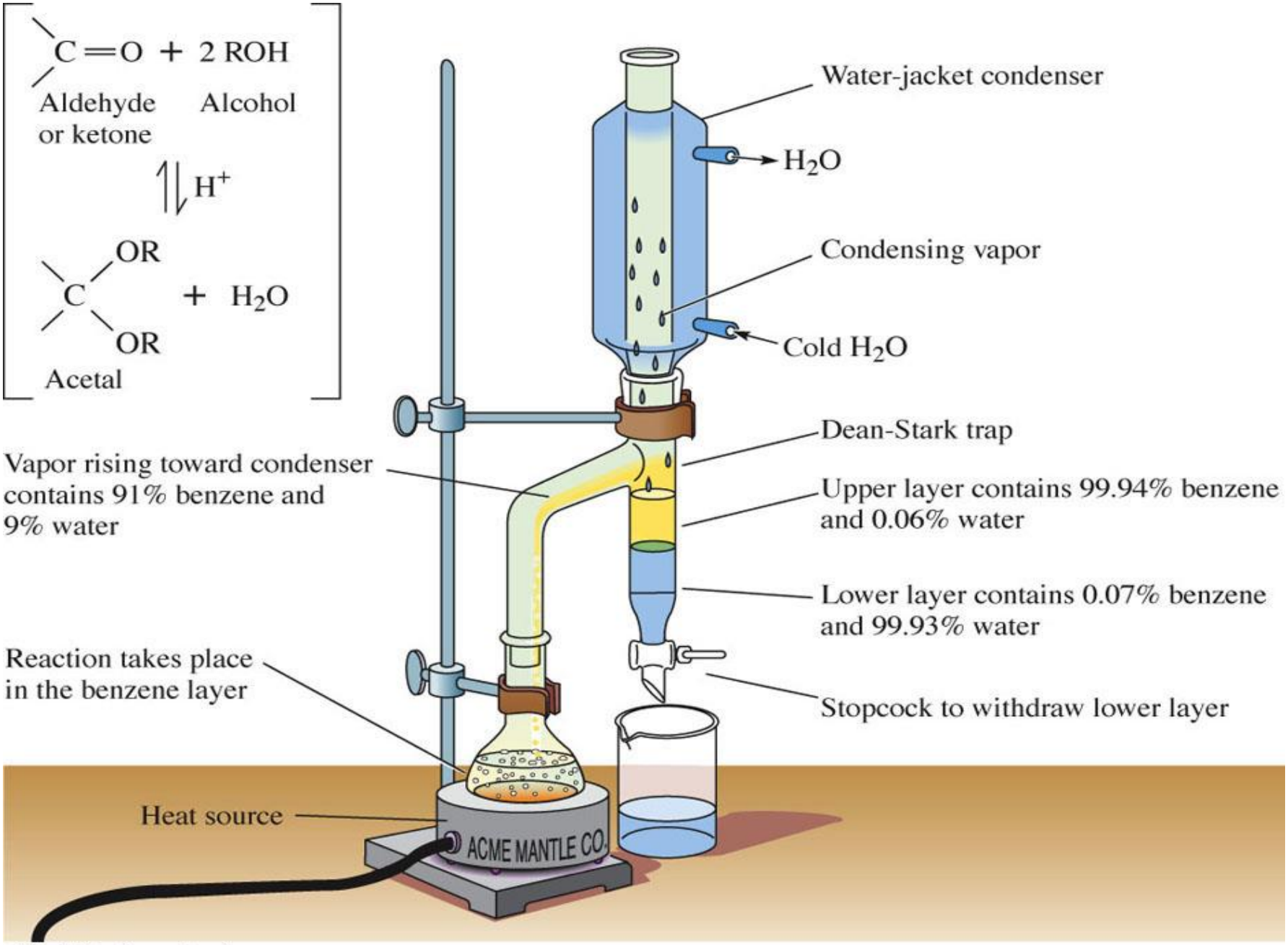


mechanism:

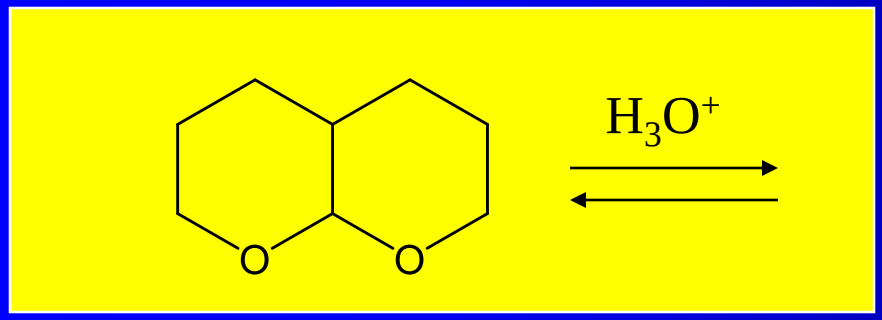
reverse of acetal formation …hemiacetal is intermediate.

application:

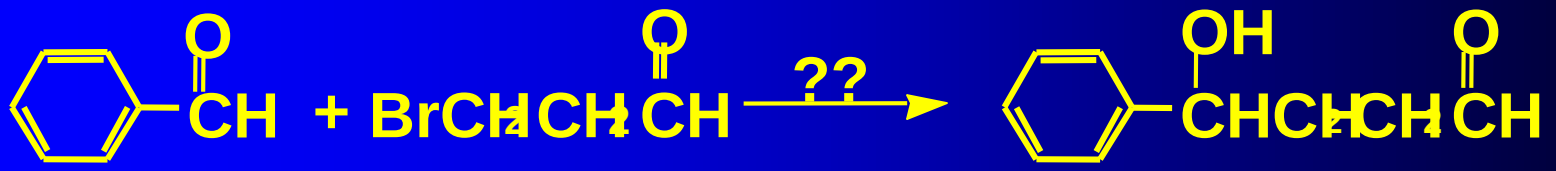
aldehydes and ketones can be "protected" as acetals.



Hydrolysis

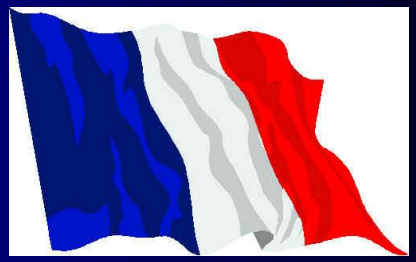


Suppose you want to make this compound?????



4-Hydroxy-4-phenylbutan

It's an alcohol. Use the Grignard Reaction!!

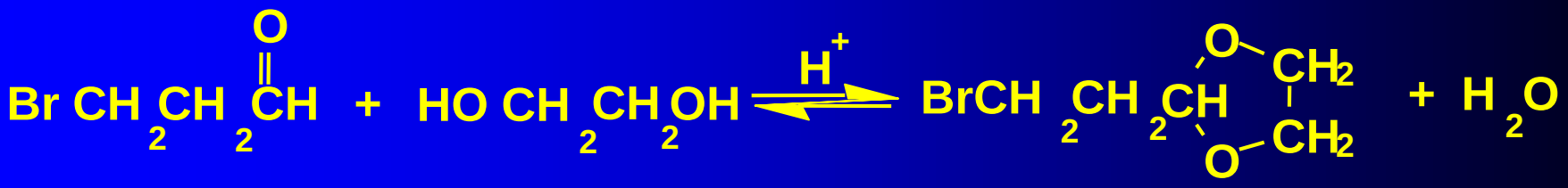


So…you got a problem with this plan ?????

Secret is….Acetals as protecting Groups

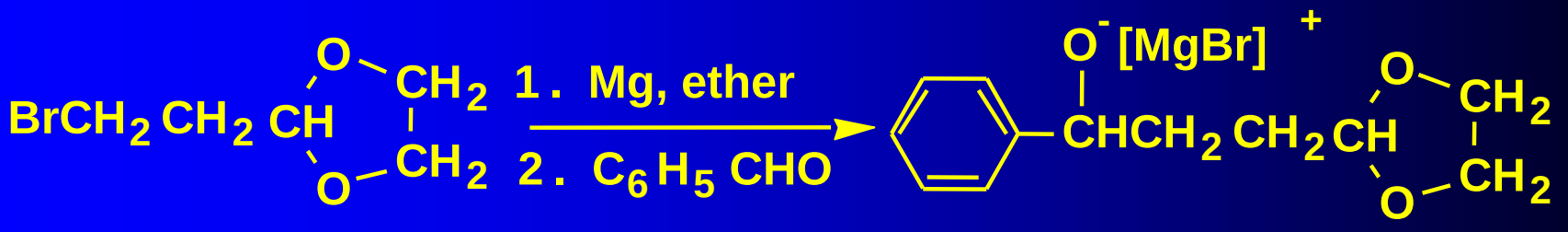
Acetals as Protecting Groups

- If the Grignard reagent were prepared from 3-bromopropanal, it would self-destruct!
- First protect the -CHO group as an acetal



Acetals as Protecting Groups

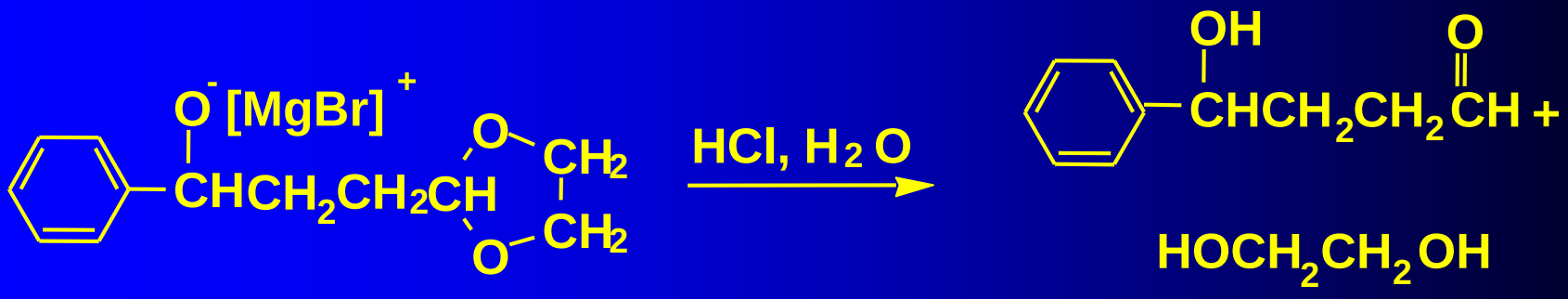
- Then do the Grignard reaction



Hydrolysis in dilute acid gives the desired product

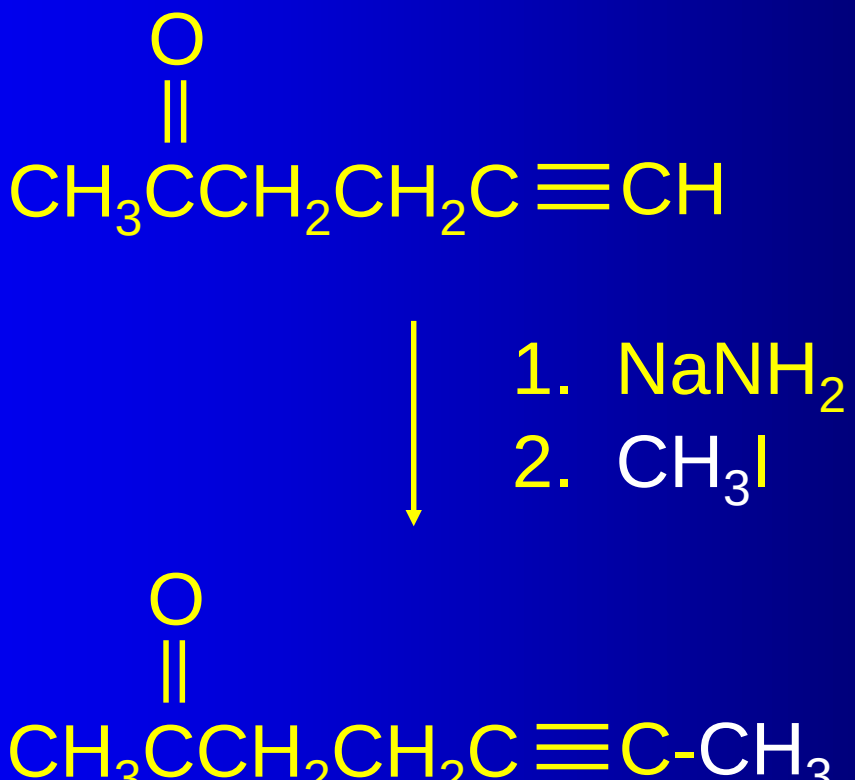
Acetals as Protecting Groups

- Hydrolysis (deprotection) regenerates the -CHO group and the hydroxyl group

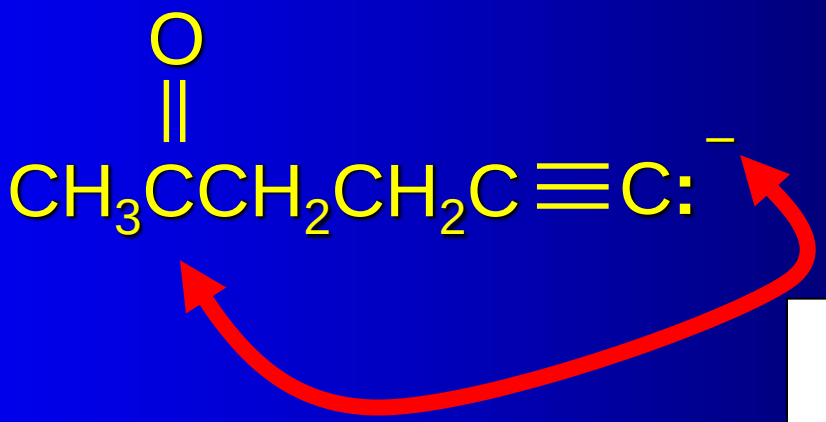


Valuable and important trick!!

For example, the conversion shown cannot be carried out directly…..why??



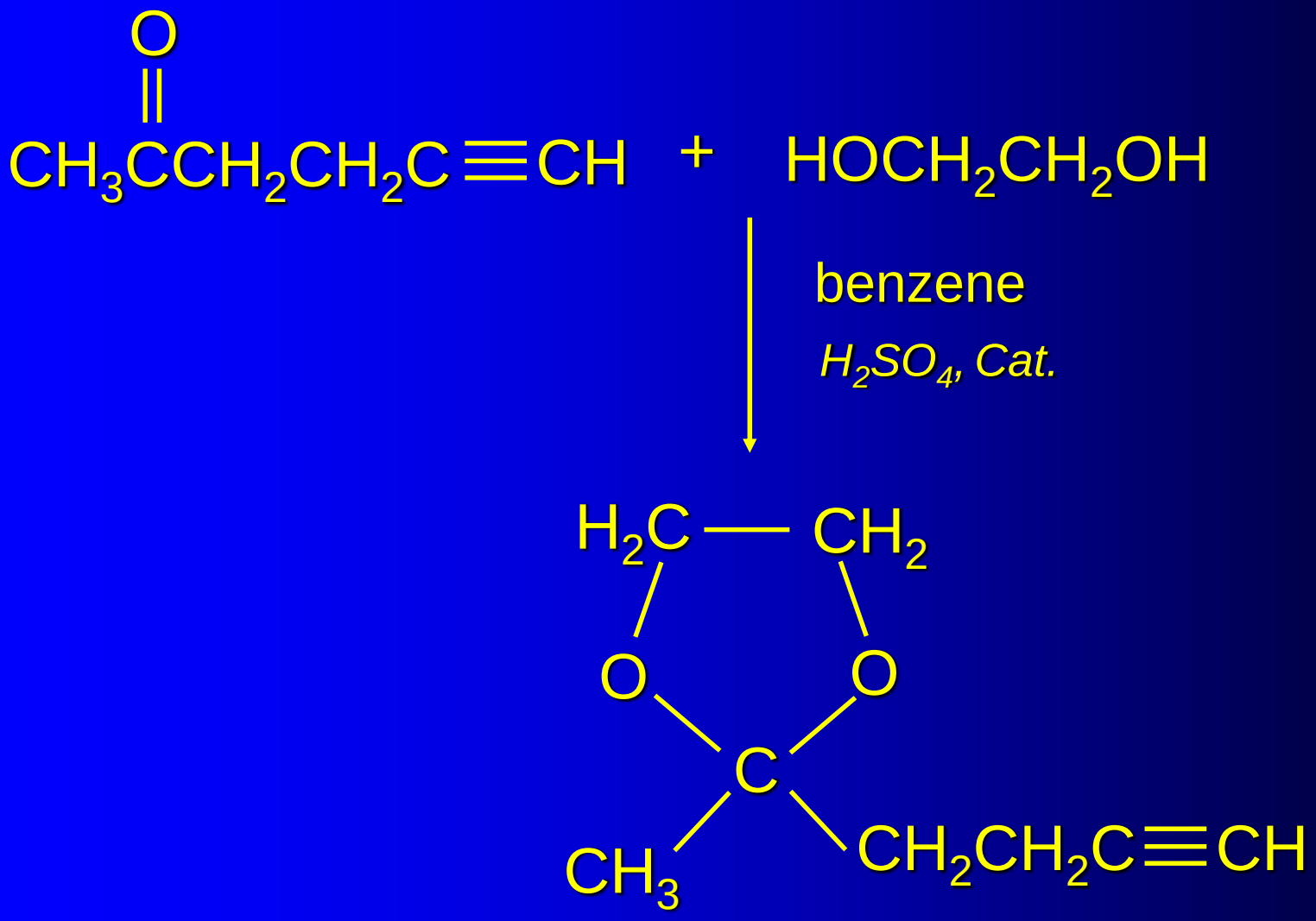
because the carbonyl group and the carbanion are incompatible…….



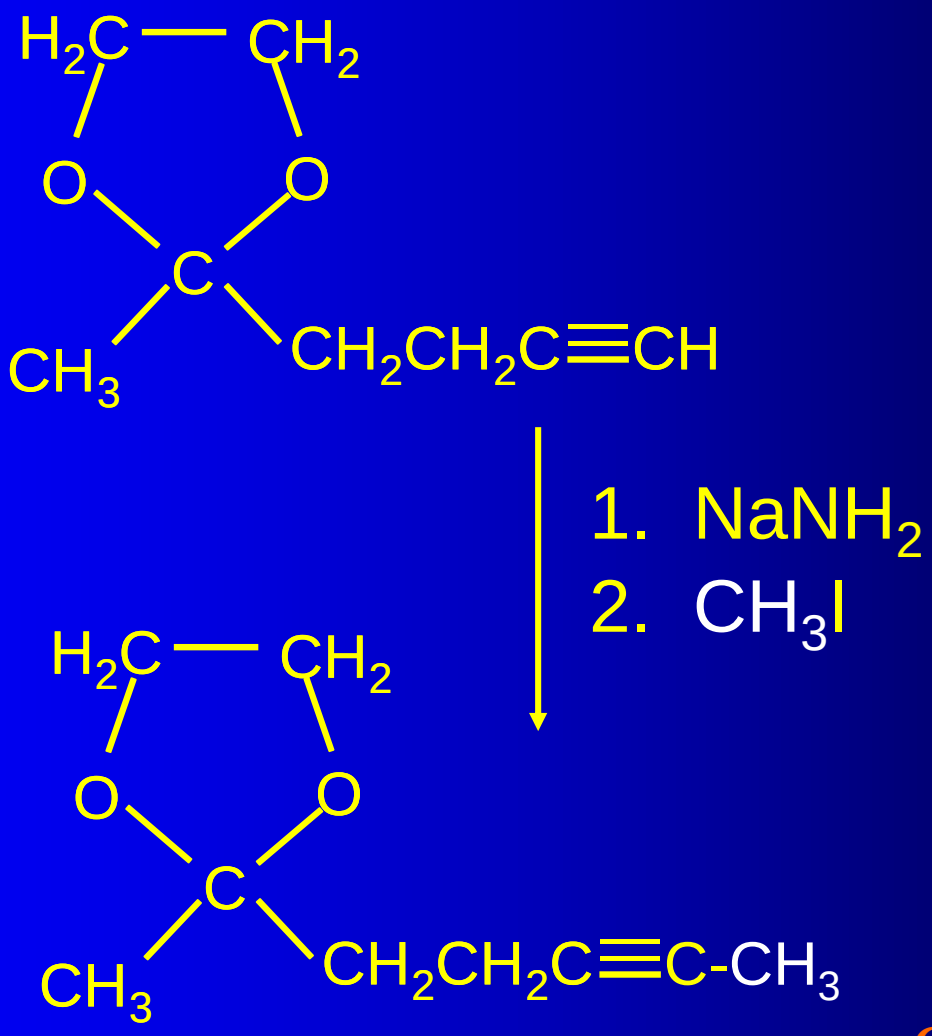
Strategy

1) protect C=O
2) alkylate
3) restore C=O

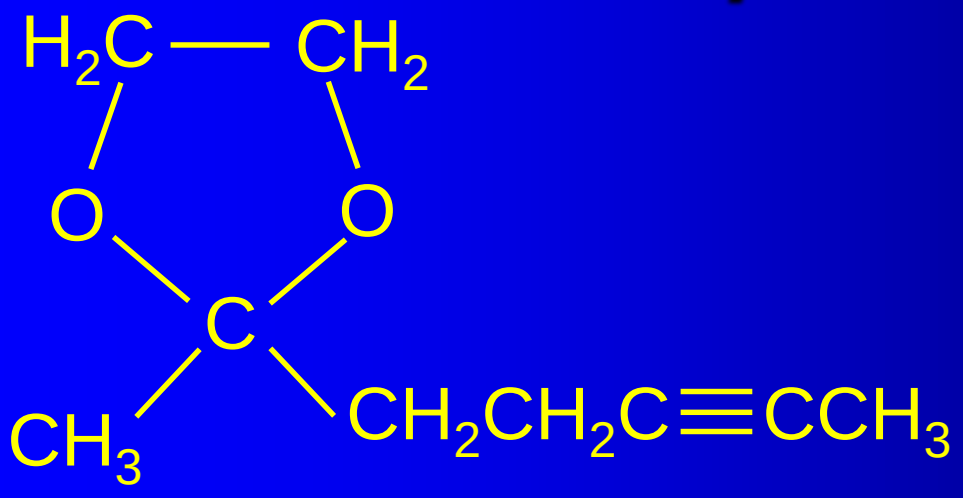
Protect


O
CH3CCH2CH2C≡CH
+
HOCH2CH2OH
benzene
H2SO4, Cat.
H2C
CH2
O
O
C
CH3
CH2CH2C≡CH

Alkylate


H2C
CH2
O
O
C
CH3
CH2CH2C≡CH
1. NaNH2
2. CH3I
H2C
CH2
O
O
C
CH3
CH2CH2C≡C-CH3

Deprotect



$\xrightarrow[HCl]{H_2O}$

$HOCH_2CH_2OH$ + $CH_3CCH_2CH_2C{\equiv}CCH_3$ (O double-bonded to the carbon adjacent to CH_3)

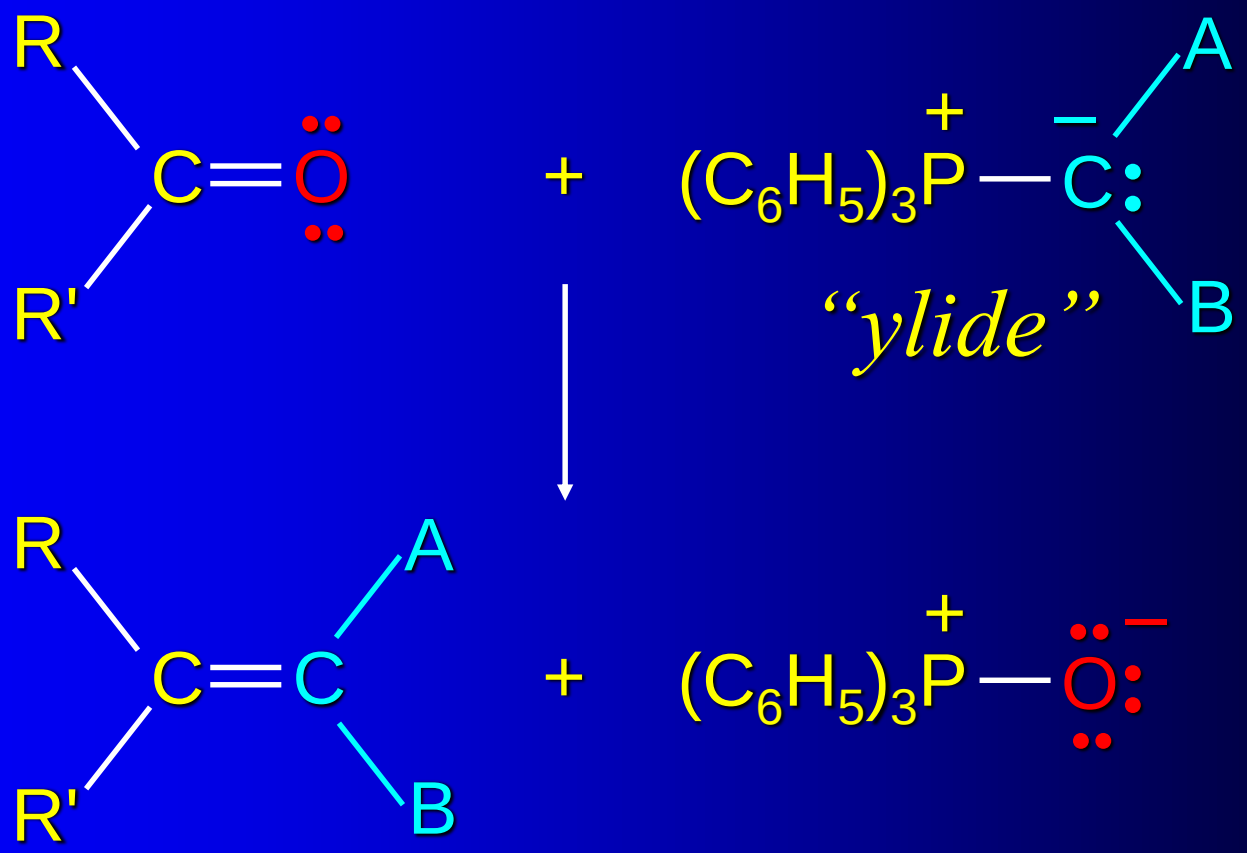
Desired product

The Nobel Prize in Chemistry 1979

Georg Wittig 1897-1987

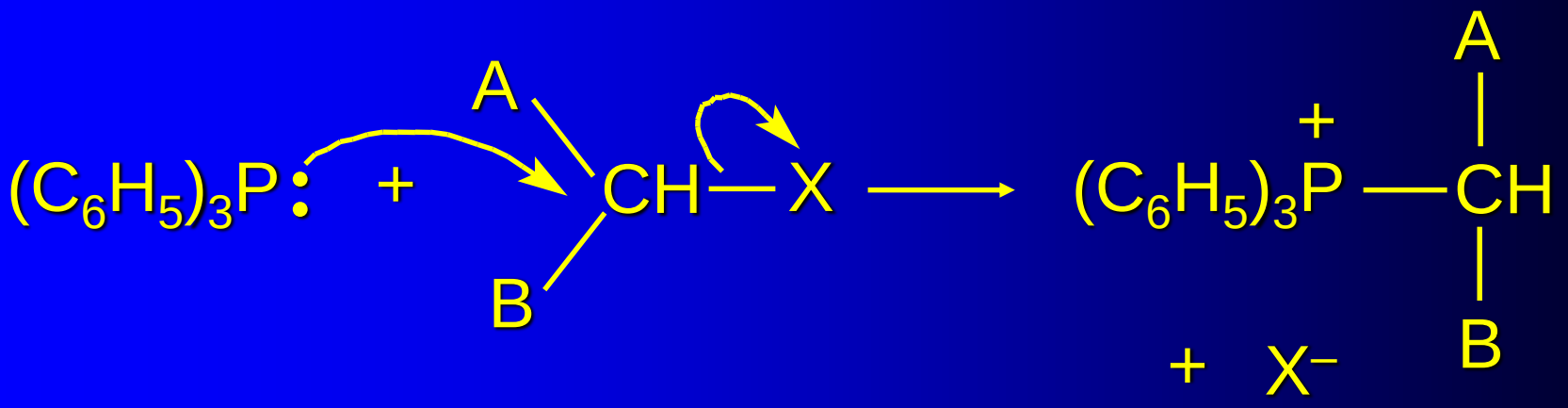
University of Heidelberg

The Wittig Reaction



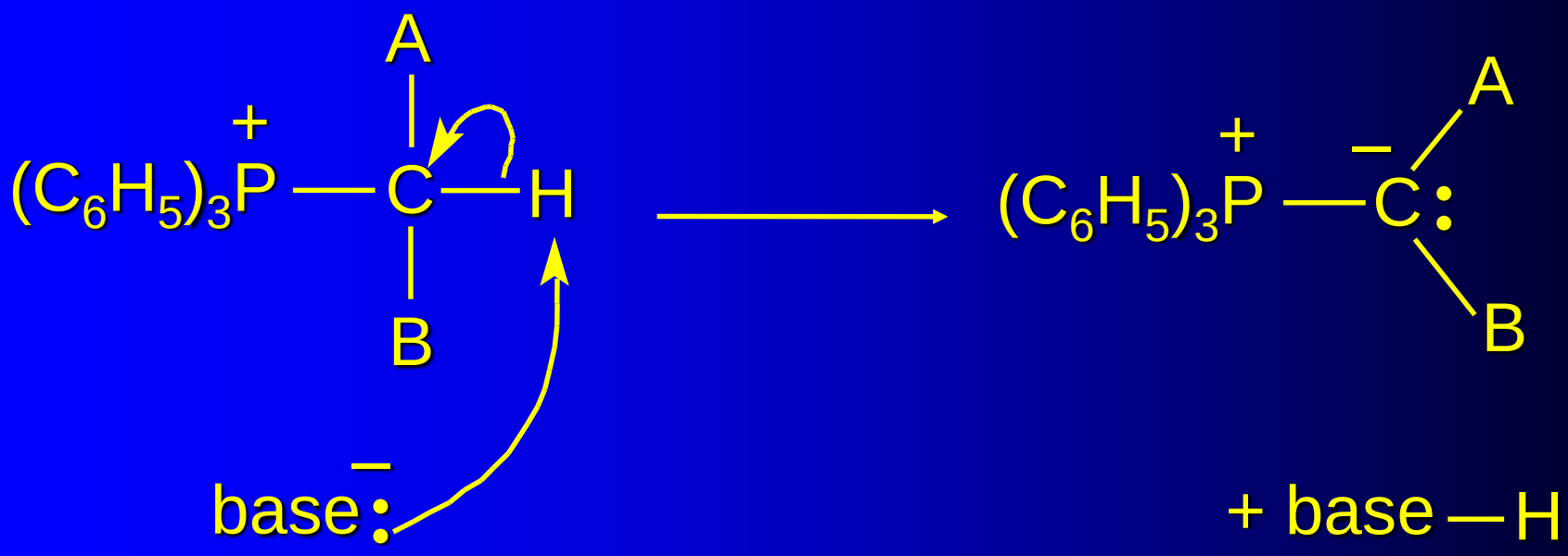
Preparation of Ylides

The ylid is made in a two step process. The first step is a nucleophilic substitution reaction that Forms a *phosphonium salt*



Preparation of Ylides

In the second step, the phosphonium salt is treated with a strong base in order to remove a proton from the carbon bonded to phosphorus.

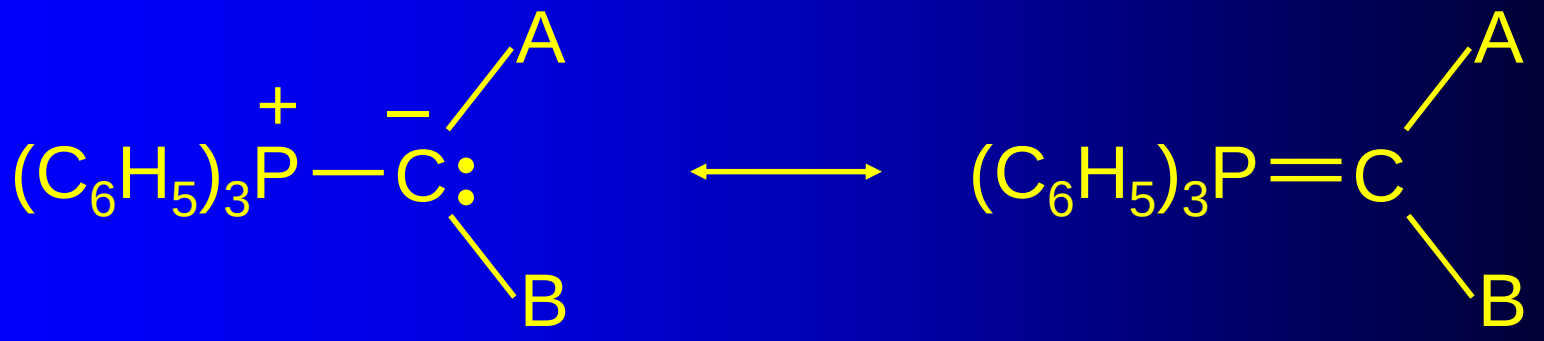


Phosphonium ylides

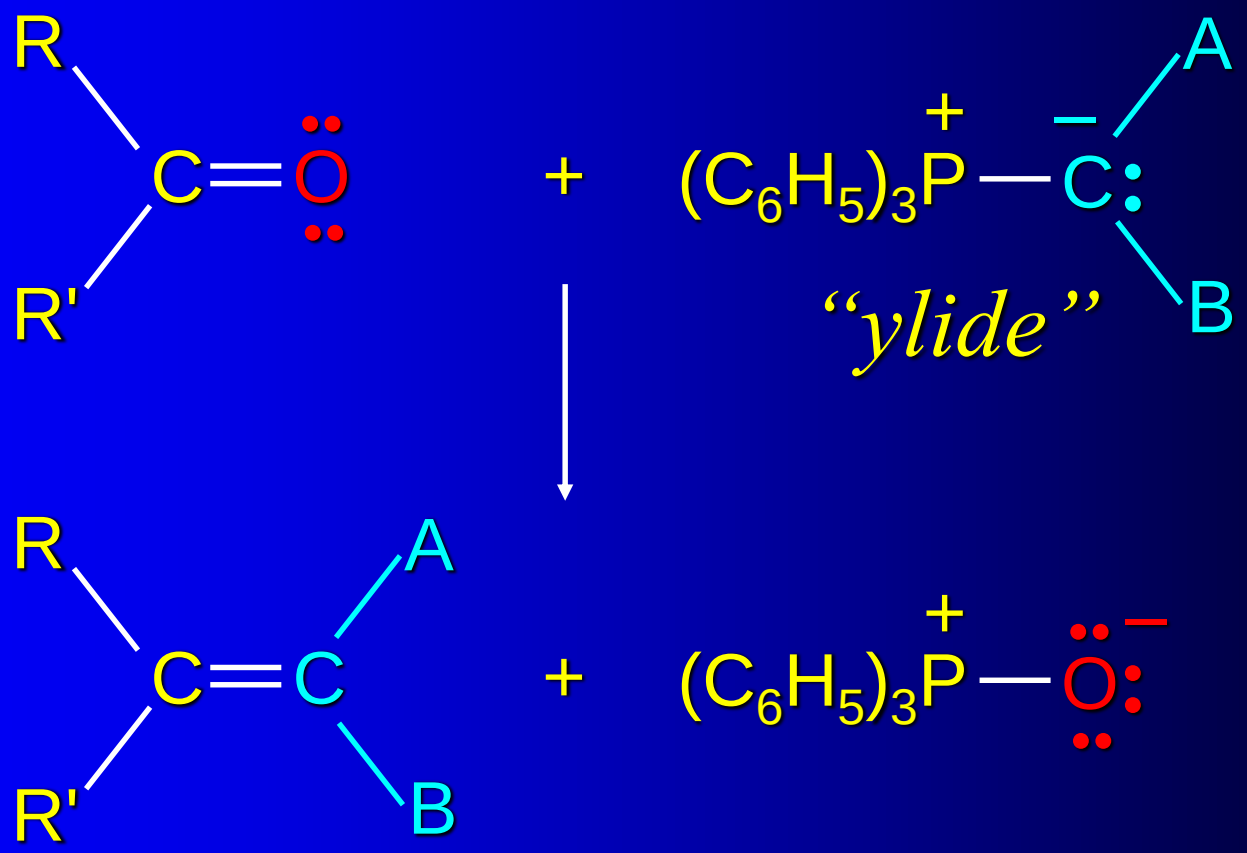
Resonance stabilized

R is usually C_6H_5 (phenyl)

Carbon is negatively polarized and nucleophilic

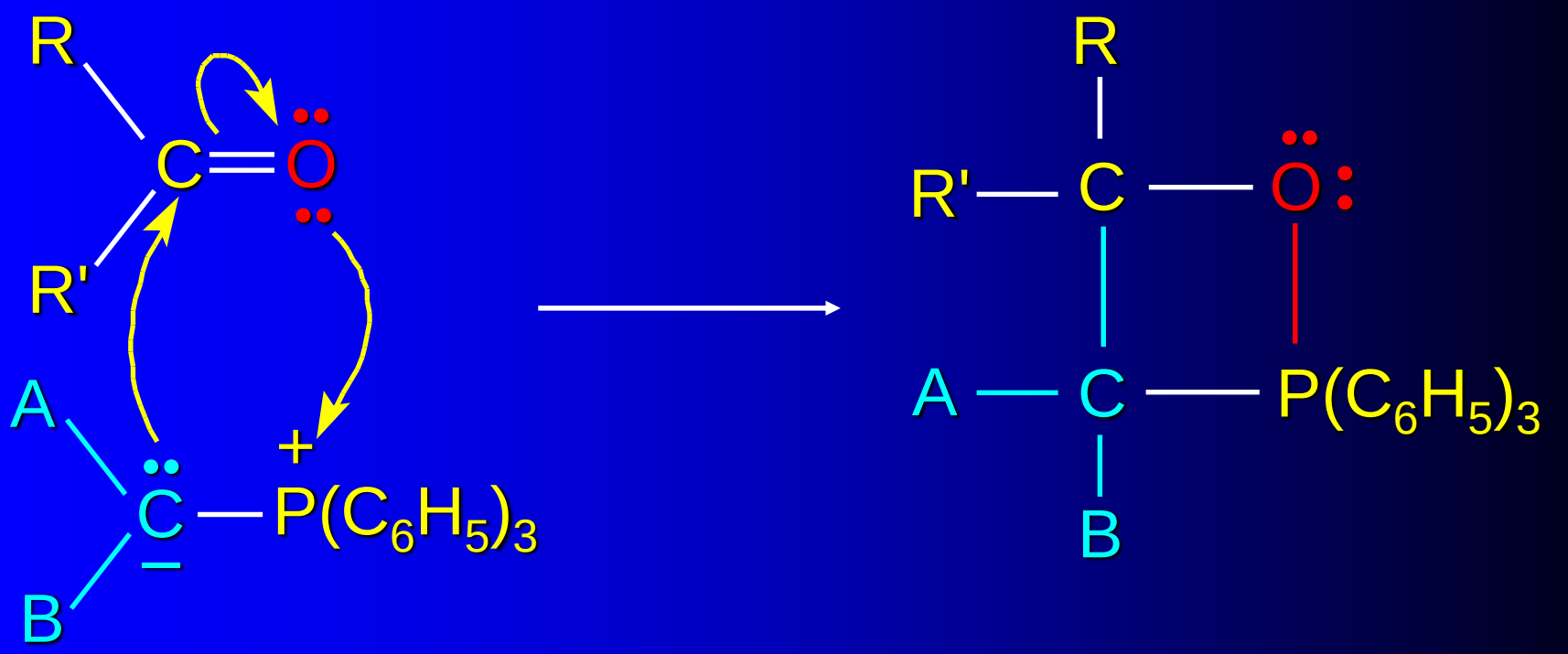


The Wittig Reaction



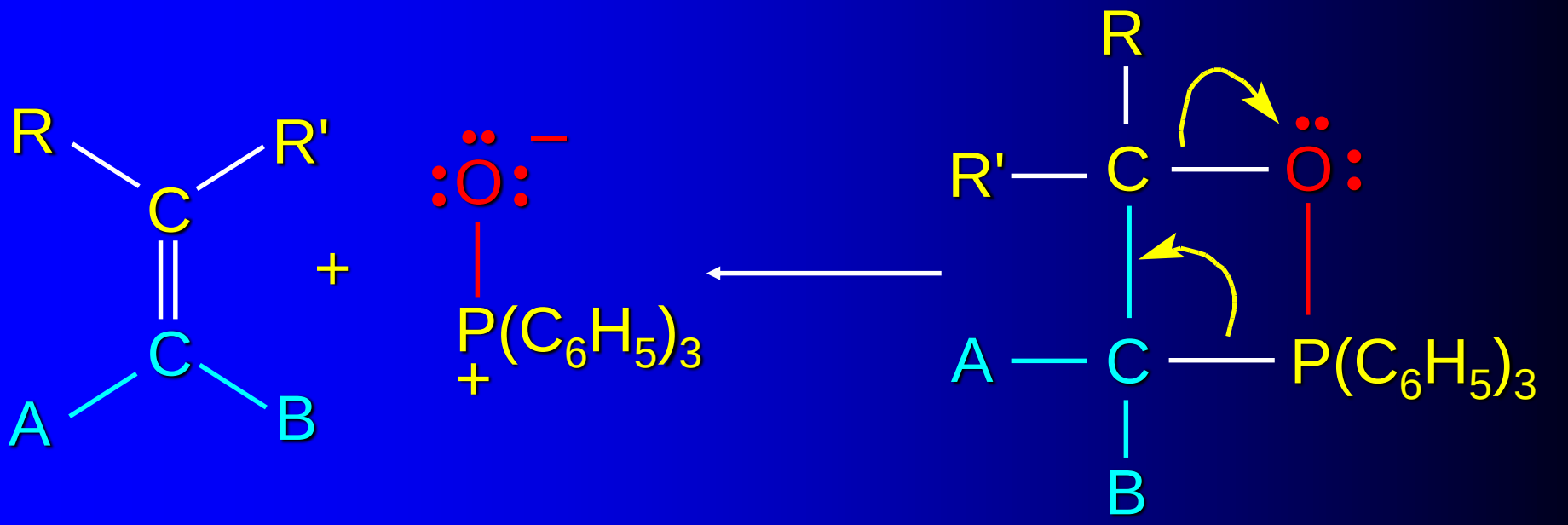
Mechanism

Step 1

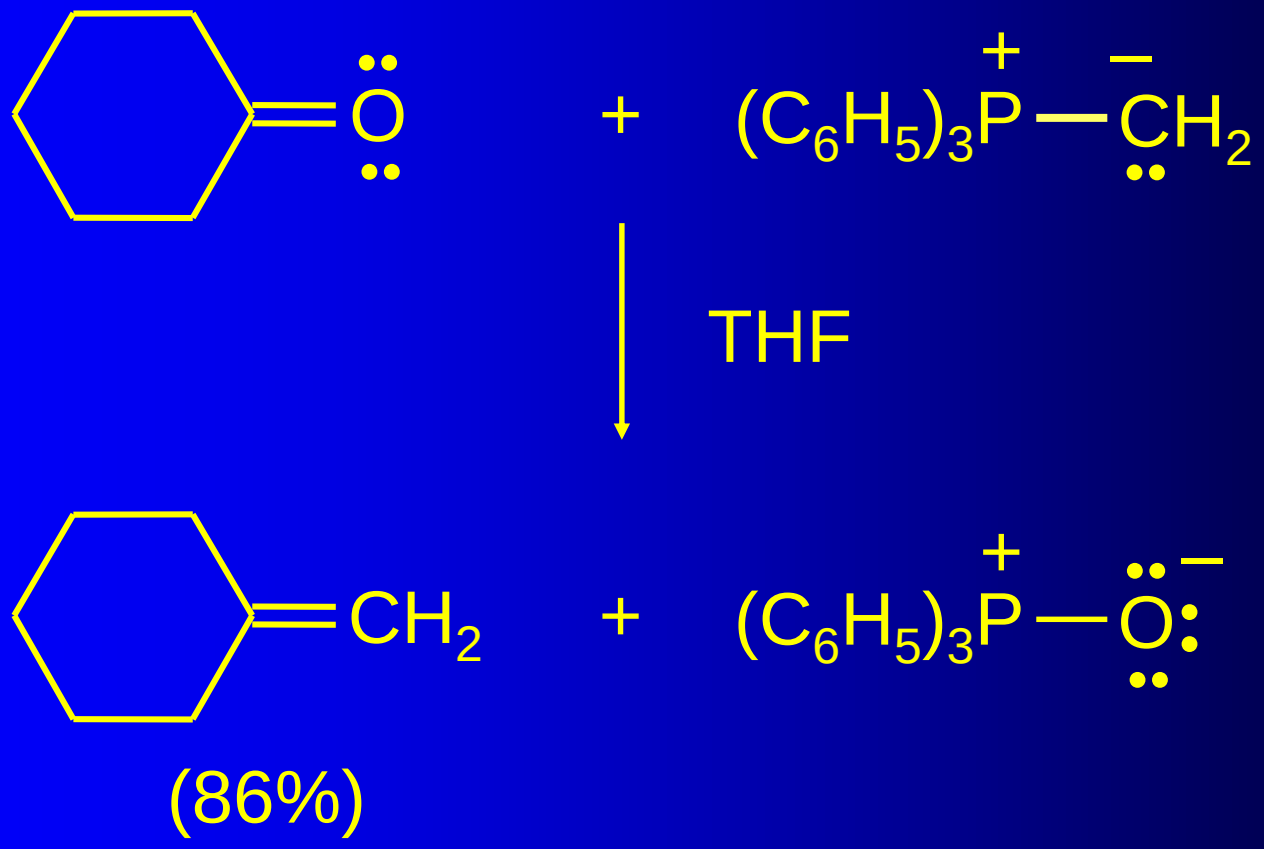


Mechanism

Step 2

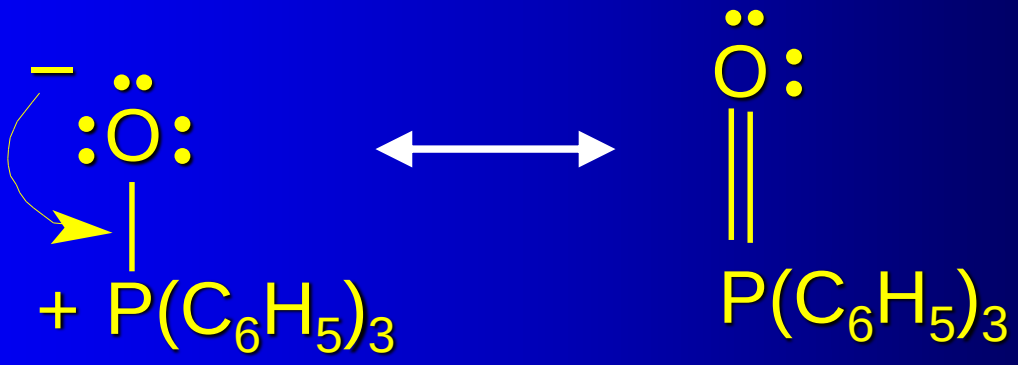


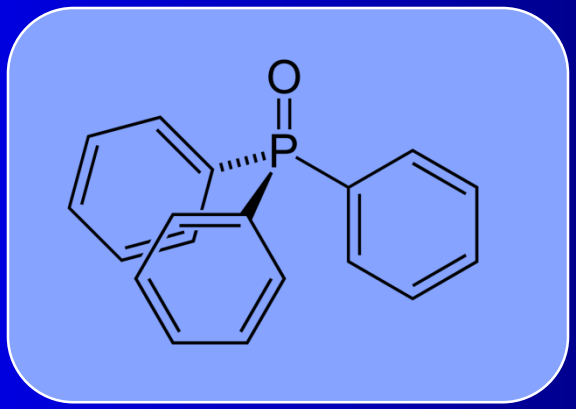
Example



(86%)

Triphenylphosphine oxide





This substance is very stable

Nearly insoluble in many solvents, i.e. pentane

Oral, mouse: LD50 = 1380 mg/kg;